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EDITORIAL

Ethical Dilemmas Regarding Treatment when Recruitment Ends in Randomized Trials

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Introduction

The ethical issues faced by clinicians have never been more challenging than they are today. For surgeons, awareness of ethical questions is perhaps even greater as they are often involved with the introduction of new techniques or technologies.

In a multicentre randomised control trial (RCT), upon the completion of recruitment and before publication of the results, there is always a period of uncertainty over the best treatment. The ethical dilemma that emerges for surgeons and their patients is what treatment should be offered during this period in view of the assumed equipoise between the conventional and new treatment.

Two good examples are the European Asymptomatic Carotid Surgery Trial (ACST)[1,2] and the Endovascular Aneurysm Repair (EVAR) Trial[3] that will not publish their results for at least 1 year after recruitment ends.

Ethical Issues Related to RCTs

The ethical basis of a RCT is that it commences with a honest null hypothesis, meaning that equipoise exists between the arms of the trial.[4,5] In trials with several arms, equipoise must exist between all arms otherwise the trial design should be modified to exclude the inferior treatment.[6] Randomised clinical trials should be constructed such that patients are given access either to the best standard therapy or to a new treatment that is considered at least equivalent or possibly superior to the standard treatment. If constructed in this way, clinical trials should be beneficial to patients.[7]

In addition, the clinician must inform suitable patients about the pros and cons of both the new and conventional treatment whilst making it clear that there is still uncertainty over the best treatment until the results are known.

The European Convention on Human Rights and Biomedicine clearly states in article 16 that research involving human subjects may only be undertaken if there is no alternative of comparable effectiveness and that the risks which may incurred by the participant are not disproportionate to the potential benefits of the research.[8] It is also assumed that the researcher acts in good faith with the interests of the profession and of the public at heart.

Clinical Practice while Awaiting the Results a RCT

For those centres not participating in a trial it seems sensible to continue their established practice until the publication of the results of the trial. However, for those centres participating in a trial the period between the end of recruitment and publication of the results poses a dilemma with regard to treatment. It remains important to remember two principles that the clinician must respect i.e. the patient's autonomy and their right to be properly informed.

Autonomy is an important ethical issue. It can be defined as the authority to make decisions in accord with one's own values, unrestrained by the values of others who do not suffer the consequences of the decision. Therefore, patients hold the authority to make health-care decisions unrestrained by the values of their clinicians, others in the healthcare industry, or the rest of society.[9] Documented informed consent

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remains an integral part of the communication between clinicians and patients.[10,11] Clinicians should remain neutral when informing patients about their treatment options. The pros and cons of each therapy should be declared without bias.

This policy of openness increases patients' satisfaction, adherence to treatment, and reduces subsequent complaints. Such a patient-centred approach is vital for the physician–patient relationship.[12] The pillars of this relationship have been summarised as the six C's: choice, competence, communication, compassion, continuity, and (no) conflict of interest.[13]

Because of the uncertainty over the best treatment during this intermediate period, both alternative treatments should continue where possible. The ability to offer both treatments will depend upon maintenance of equipoise and funding. Both the clinician and patient need to remain in equipoise with regard to the conventional and new treatment. This should present less of a problem for the clinician, as the trial would have been stopped prematurely by the data monitoring committee if there had been a clear advantage of one treatment over the other.

The EVAR and carotid stenting trials[14] are those that are currently 'stealing the show'. Rumours about the likely results of such trials are often available to patients, especially via the Internet, which usually favours the new treatment. Such new treatments are also promoted by the commercial sector, which have a vested financial interest. For instance, while some reservations have been expressed from some researchers on the wide applicability of the results of the SAPPHIRE study (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy),[15] it is anticipated that these results will be used to grant a Premarket Approval (PMA) for the devices employed in this FDA-approved trial. This ultimately would result in easy availability of the devices and liberalisation in the indications for carotid stenting.[14] Therefore, it is the clinicians' responsibility to ensure that patients are not unduly biased by potentially inaccurate information.

Continued funding of the new treatment is another prerequisite. Many new treatments, such as EVAR, may be more expensive than conventional treatment. Therefore, funding agencies may be reluctant to continue funding once recruitment has finished until the results are known. This issue should be addressed and incorporated into the trial design. A good example is the EVAR trial where funding of the new treatment, and randomisation, will continue after the end of the trial until the results are published. This additional data will not contribute to the initial results but will be incorporated into subsequent analysis.

Conclusion

Because of the uncertainty over the best treatment after the end of recruitment in RCTs and until the publication of the results, both the new and the conventional treatments should be offered, based on continued equipoise. This issue should be addressed in the design of the RCTs as to ensure adequate funding. Patient's autonomy and their right to be properly informed should always be respected. For this reason, clinicians should ensure that patients receive accurate information, not biased by the media and non-professional sources.

References

1 Halliday AW, Thomas D, Mansfield AO, for the Steering Committee. The Asymptomatic Carotid Surgery Trial (ACST). Rationale and design. *Eur J Vas Surg* 1994;**8**:703–710.
2 MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal stroke by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;**263**:1491–1502.
3 Brown LC, Epstein D, Manca A, Beard JD, Powell JT, Greenhalgh RM. The UK endovascular aneurysm repair (EVAR) trials: design, methodology and progress. *Eur J Vasc Endovasc Surg* 2004;**27**:372–381.
4 Levine RJ. *Ethics and regulations of clinical research*. 2nd ed. Baltimore, MD, Urban and Schwarzenberg, 1986.
5 Idem. The use of placebos in randomised clinical trials. IRB: A Reviews of Human Subjects Research. 1985;**7**:1–4.
6 Freedman B. Equipoise and the ethics of clinical research. In: Kuhse H, Singer P, eds. *Bioethics. An anthology.* Oxford: Blackwell Publishers, 1999:429–435.
7 Levine RJ. Ethics of clinical trials: do they help the patient? *Cancer* 1993;**72**:2805–2810.
8 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. European Council, Oviedo 1997; 4.IV.
9 Schwartz RL. Autonomy, futility, and the limits of medicine. In: Kuhse H, Singer P, eds. *Bioethics. An anthology.* Oxford: Blackwell Publishers, 1999:518–522.
10 Mavroforou A, Giannoukas AD, Katsamouris AN, Michalodimitrakis E. The importance of communication between physicians and patients. Special considerations in the era of endovascular therapy. *Int Angiol* 2002;**21**:99–102.
11 Mavroforou A, Giannoukas AD, Mavrophoros D, Michalodimitrakis E. Physicians' liability in interventional radiology and endovascular therapy. *Eur J Radiol* 2003;**46**:240–243.
12 British Medical Association Ethics Department. The doctor–patient relationship.*Medical ethics today. The BMA's handbook of ethics and law.* 2nd ed, 2004:23–70.
13 Emanuel EJ, Dubler NN. Preserving the physician–patient relationship in the era of managed care. *JAMA* 1995;**273**:323–329.
14 Hobson II RW. Rationale and status of randomised controlled clinical trials in carotid artery stenting. *Semin Vasc Surg* 2003; **16**:311–316.
15 Yadav JS. Stenting and angioplasty with protection in patients at high risk from endarterectomy: the SAPPHIRE study. American Heart Association. *Circulation* 2002;**106**:2986a.

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